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GLOSSARY

Abbreviation	Definition
ACR	American College of Rheumatology
APS	American Pain Society
BID	Two Times per Day
BUN	Blood Urea Nitrogen
COX	Cyclooxygenase
DMARD	Disease-Modifying Antirheumatic Drug
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HAQ	Health Assessment Questionnaire
IND	Investigational New Drug Application
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LS Mean	Least Square Mean
MI	Myocardial Infarction
NDA	New Drug Application
NSAID	Non-steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OASI	Osteoarthritis Severity Index
PD	Pharmacodynamic
PG	Prostaglandin
PID	Pain Intensity Difference
PK	Pharmacokinetic
PR	Pain Relief
PRA	Plasma Renin Activity
PRID	Sum of Pain Relief and Pain Intensity Difference
PRN	As Needed
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Once per Day
QID	Four Times per Day
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
SD	Single Dose
TID	Three Times per Day
Tx	Thromboxane
UGI	Upper Gastrointestinal
URTI	Upper Respiratory Tract Infection
VAS	Visual Analog Scale
WBC	White Blood Cell
WOMAC	Western Ontario and McMaster Universities OA Index

1.0 OVERVIEW

Celecoxib (tradename Celebrex™) is a specific cyclooxygenase-2 (COX-2) inhibitor with anti-inflammatory and analgesic activity.

Non-steroidal anti-inflammatory drugs (NSAIDs) possess anti-inflammatory, analgesic, and antipyretic activity, and are widely used to treat osteoarthritis (OA), rheumatoid arthritis (RA), and pain. However, these agents cause upper gastrointestinal (UGI) mucosal damage and side effects related to platelet and renal function that limit use in a significant number of patients. (2-4) NSAIDs are known to inhibit the enzyme cyclooxygenase (COX) resulting in a reduction in prostaglandin (PGs) production. (5,6) Recently, two distinct COX isoforms were identified: 1) a constitutive form (COX-1), present in most tissues including the GI mucosa and platelets, that produces PGs necessary for normal physiological function (6,7) and 2) an inducible form (COX-2) that is primarily expressed in association with inflammation. (8,9) Our hypothesis is that constitutive COX-1 activity protects the GI tract and maintains normal platelet function whereas inducible COX-2 activity is responsible for inflammation and pain. Therefore, specific inhibitors of COX-2 will be anti-inflammatory and analgesic without having the mechanism-based side effects of NSAIDs.

Nonclinical in vitro and in vivo studies have demonstrated that celecoxib is a specific inhibitor of COX-2. (10) In animal studies, celecoxib was shown to have anti-inflammatory and analgesic effects equivalent to NSAIDs, and to inhibit maximally COX-2 derived PG formation while sparing PG production in the GI tract. The compound underwent extensive toxicological evaluations, including acute, subchronic, chronic, genetic, and reproductive toxicology, as well as carcinogenicity testing. No novel toxicity was observed, and the established safety margins suggested that celecoxib had a pharmacological profile that would allow rigorous testing in humans.

Subsequently, the clinical development program was undertaken to:

- determine the pharmacokinetic properties of celecoxib in humans;
- establish the efficacy of celecoxib in treating the signs and symptoms of OA and RA;
- establish the efficacy of celecoxib in the management of pain;

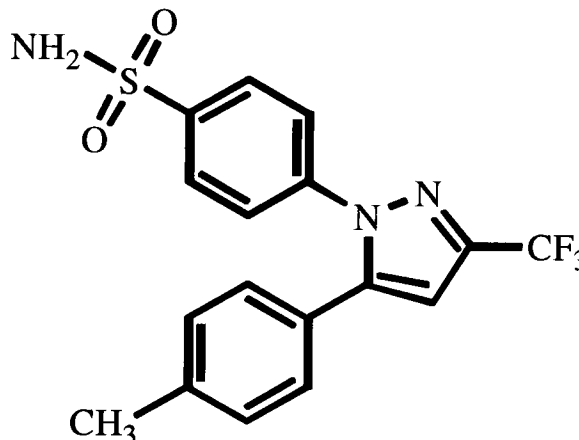
- compare the effects of celecoxib with that of NSAIDs and placebo on the UGI mucosa, platelet function, and renal function; and
- assess the safety and tolerability of celecoxib in patient populations in whom its use is indicated.

2.0 BACKGROUND

2.1 Pharmacological Class

Celecoxib is a novel diarylsubstituted pyrazole that selectively inhibits COX-2. The chemical name of the compound is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide. Celecoxib has a molecular weight of 381.38. The chemical structure is depicted in Figure 1.

Figure 1. Chemical Structure of Celecoxib (C₁₇H₁₄F₃N₃O₂S)



Celecoxib selectively inhibits COX-2 through the time-dependent formation of a tight enzyme-inhibitor complex that is noncovalent but slowly dissociable. Celecoxib has a low affinity for the constitutively expressed isoform COX-1. Consequently, at therapeutic doses, celecoxib has no measurable effect on prostanoids synthesized by COX-1 and does not interfere with normal COX-1 regulated processes.

The World Health Organization (WHO) working group on anatomical therapeutic chemical (ATC) classification recently assigned selective inhibitors of COX-2 to a new ATC category for anti-inflammatory agents. The category recognizes the differentiation of COX-2 inhibitors from classic NSAIDs on the basis of their pharmacologic activity.

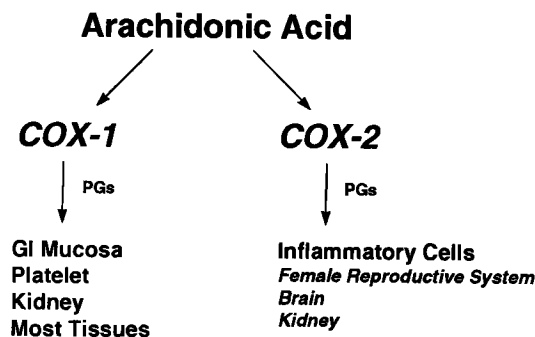
2.2 Scientific Rationale

2.2.1 Mechanism of the Inherent Risks of Current Therapy

Currently, NSAIDs are the most common class of agents used to treat the signs and symptoms of arthritis and pain. The NSAIDs act via inhibition of the formation of prostanoids from arachidonic acid by COX. (5,6) Prostaglandins (and thromboxane, which is derived from PGH₂) are produced by all tissues as locally acting autacoids, and are important for many physiological functions in the GI tract, kidney, reproductive system and in platelets. (6) Prostaglandins are also key mediators of inflammation and pain, (6) and inhibition of their production by NSAIDs provides therapeutic benefit in many clinical conditions. However, NSAIDs pose a risk for GI, platelet and renal side effects because their mode of action results in unavoidable, mechanism-based adverse effects, (2-4) due to the concomitant reduction of inflammatory PGs and PGs important for normal physiological function. Recently, two distinct isoforms of COX were identified and designated COX-1 and COX-2. (6-9) These two isoforms are closely related and perform identical catalytic reactions with arachidonic acid, but the tissue distribution and regulation of expression of each are widely divergent.

Currently available NSAIDs inhibit both COX isoforms with negligible specificity in vitro (<10 fold). (1) COX-1 is constitutively expressed in most tissues throughout the body, including the GI tract, kidney, and platelets. (6,7) In contrast, COX-2 is normally expressed in very low amounts in healthy tissue, but is induced to high expression by inflammatory mediators (Figure 2). (8,9) Notably, the induced expression of COX-2 can be prevented by anti-inflammatory glucocorticoids. (11) The expression of COX-2 in association with inflammation, as well as pharmacological studies in animals, suggest that the therapeutic benefits of NSAIDs are largely due to the inhibition of COX-2. In contrast, the GI and platelet toxicity caused by NSAIDs is due to inhibition of COX-1, which is predominantly expressed in these tissues. Because COX-2 is constitutively expressed in the kidney, (12) the degree to which the renal effects of NSAIDs can be ascribed to COX-1 is uncertain, and studies in animals have not provided definitive information.

Figure 2. COX Isoforms



2.2.2 Beneficial Mechanism of Selective COX-2 Inhibition

The hypothesis presented in Figure 2 suggests that an agent which specifically inhibits COX-2, while sparing COX-1 activity, would provide the anti-inflammatory and analgesic activity of NSAIDs without their mechanism-based side effects. A number of studies in animal models with agents demonstrated to selectively inhibit COX-2 have supported this hypothesis. (10,13)

These observations led to the development of celecoxib, a potent and specific COX-2 inhibitor. Under a wide variety of in vitro conditions celecoxib demonstrates high selectivity for COX-2 (300 to over 2000 fold separation in inhibition curves vs. COX-1). The COX-2 specificity of celecoxib is due to an ability to occupy space within the active site of this isoform that is not present in COX-1. This unique binding to the active site results in the formation of a tight enzyme-inhibitor complex that is only slowly dissociable and non-competitive with substrate. In contrast, inhibition of COX-1 observed with high concentrations of celecoxib displays conventional competitive kinetics. The novel kinetic behavior of celecoxib noted in vitro translates to specific inhibition in vivo, i.e. in animals, concentrations/doses of celecoxib that maximally inhibit COX-2 derived PG formation have little or no effect on PG formation by COX-1 in platelets, kidney or the GI mucosa.

2.3 Intended Use

Celecoxib is intended for use in the treatment of the signs and symptoms of OA and RA and for the management of pain. The potential clinical benefits include antiarthritic and analgesic efficacy without UGI ulceration, ulcer complications or platelet dysfunction.

3.0 NONCLINICAL PHARMACOLOGY, TOXICOLOGY AND PHARMACOKINETICS

3.1 Nonclinical Pharmacology

Celecoxib was evaluated in a series of nonclinical pharmacology studies to: 1) examine its inhibitory kinetics and mechanism of action; 2) determine its anti-inflammatory and analgesic actions in animal models *in vivo*; and 3) specifically evaluate its propensity to cause GI tract injury and to explore its potential for action on a variety of physiological systems that are targets of NSAIDs. A major goal of these studies was to understand the pharmacological action of celecoxib in relation to its ability to produce differential inhibition of COX isoforms, *in vitro* and *in vivo*.

Celecoxib selectively inhibited COX-2 activity when tested *in vitro* on human recombinant COX-1 and COX-2. The two major metabolites of celecoxib did not inhibit either COX-1 or COX-2 *in vitro*, indicating that levels of celecoxib achieved *in vivo* likely determine the extent of COX-2 inhibition.

In other *in vitro* studies with whole blood, celecoxib inhibited lipopolysaccharide (LPS)-stimulated PGE₂ synthesis by monocytes (COX-2 mediated) at concentrations considerably lower than those needed to inhibit ionophore-stimulated synthesis of TxB₂ (COX-1 mediated). Celecoxib showed little ability to inhibit 5-lipoxygenase, the rate limiting enzyme for leukotriene synthesis in the other arm of the arachidonic acid metabolic pathway.

Celecoxib was evaluated in animal models known to be sensitive to NSAIDs, and which have been shown to be predictive of activity in humans. In an acute inflammation model, celecoxib caused dose dependent inhibition of swelling and hyperalgesia (pain) caused by an irritant, with maximal efficacy similar to that achieved with NSAIDs. Hyperalgesia was also rapidly reversed in this model by celecoxib, with a concomitant reduction in local inflammatory PG levels, as well as PG levels in cerebrospinal fluid. In a model of arthritis, celecoxib dose dependently reversed inflammation, local PG production and PG formation in cerebrospinal fluid. These data suggest that inhibition of COX-2 derived PG production by celecoxib is sufficient to achieve all of the anti-inflammatory and analgesic activity of mixed COX-1/COX-2 inhibitors (NSAIDs), and are consistent with the hypothesis that the therapeutic activity of the latter agents results

from inhibition of COX-2. Celecoxib also showed analgesic and anti-pyretic activity in other standard animal models.

In other studies in rodents, celecoxib was shown to have minimal effects on gastric PG production and did not cause GI lesions at doses >10 fold in excess of the maximal dose needed for anti-arthritic activity, and did not alter renal PG production as assessed in the urine.

3.2 Toxicology

A comprehensive non-clinical safety program designed to support clinical testing with celecoxib in chronic indications in adults has been completed. This program included toxicology studies for durations of up to six months in rodents and up to one year in dogs, and carcinogenicity studies conducted in rodents. Other studies were conducted to evaluate the acute lethal potential of celecoxib and adverse effects on physiological systems resulting from the pharmacological action of the compound. Potential reproductive toxicity was evaluated in studies that collectively addressed male and female reproductive function beginning with mating and early pregnancy through multiple generation assessments of reproductive performance. Mutagenic potential was evaluated in vitro using both mammalian and non-mammalian test systems; clastogenic potential was evaluated in vitro and in vivo. Other studies were conducted to characterize the irritation and antigenic potential of the compound.

In both rodents and dogs, the dose limiting toxicity observed in safety studies with celecoxib was related to the GI tract. At high doses and exposures of celecoxib, GI injury similar to that observed with NSAIDs was observed. The plasma concentrations/exposures of celecoxib at which such injury was observed were similar in rats and dogs and were at least 4-to 9-fold higher than are needed to achieve maximal anti-arthritic activity in humans. This is consistent with the COX selectivity of celecoxib, i.e., at greater than therapeutic concentrations of celecoxib, COX-1 is inhibited and GI lesions ensue. This contrasts with NSAIDs, where therapeutic doses are lethal in rats and dogs. (14) Celecoxib did not cause renal papillary necrosis, dystocia, or affect hemostasis, all typical effects of NSAIDs. Celecoxib was not mutagenic and was not carcinogenic in rodents.

No evidence of toxicity or adverse pharmacological effects was produced by celecoxib in rats or dogs at the expected exposures and maximal plasma concentrations of the clinical doses (200 and 400 mg/day).

Based on the toxicity profile of celecoxib in animals, celecoxib is clearly differentiated from NSAIDs and is considered safe for use in humans.

3.2.1 Carcinogenicity

The carcinogenicity evaluation of celecoxib in mice was made at average exposures that were approximately 1- to 2.5-fold greater in males and 1- to 2-fold greater in females than the exposures at the clinical dose range. The carcinogenicity assessment of celecoxib in rats was made at average exposures throughout the study were as high as 4-9-fold greater in males and 5-10-fold greater in females than the exposures produced by the range of clinical doses.

Carcinogenicity evaluations in rats and mice revealed no evidence of carcinogenicity or increases in the incidence of background tumors after 104 weeks of dosing.

3.2.2 Reproductive Toxicity

Celecoxib does not produce any effect on fertility or male reproductive function in rats. Assessments of reproductive function and early embryonic development show that decreased embryonic viability reflected as pre- and post-implantation loss is produced by the compound at dosages greater than 50 mg/kg/day, which produced exposures greater than therapeutic exposures (5-11-fold the area under the plasma concentration-time curve from 0-24 hours at the range of clinical doses). The same effects are seen with NSAIDs. This is the likely consequence of disruption of prostaglandin-dependent processes involved in early reproductive function and the establishment of pregnancy. No evidence of an effect on ovulation was observed, but the finding of dose-dependent decreases in numbers of implantation sites and increases in resorptions suggest that, in the rat, implantation and maintenance of pregnancy may be affected by celecoxib. The effects are expected given the pharmacological action of the compound (i.e., PG inhibition) and are not due to permanent alteration of female reproductive function.

Teratology evaluations conducted in rabbits did not reveal evidence of teratogenicity for celecoxib at dosages up to 150 mg/kg/day. A higher dosage (300 mg/kg/day) produced post-implantation loss.

Studies in rats confirmed that celecoxib crosses the placenta and is available to the fetus. Diaphragmatic hernia was observed in one of two teratology studies conducted in rats at exposures that were at least 7-fold greater than the exposure associated with the maximum clinical dose, 400 mg/day. This malformation is not the same as the more severe presentation involving lung malformations typically seen congenitally in humans; this effect is not regarded as a teratogenic mechanism, but rather as an exacerbation of the background incidence of this malformation in the rat.

The dosages used in the perinatal evaluation produced evidence of maternal toxicity in the F₀ females as mortality related to GI lesions and/or peritonitis and decreased feed consumption in the higher dose groups. The length of gestation was slightly but significantly increased for all celecoxib-treated groups but not in a dose-dependent manner and all gestation periods were within historical control data ranges. There was no evidence of dystocia or increased parturition time. There was no evidence of an effect of celecoxib on the physical appearance of the pups with the exception of diaphragmatic hernias discussed previously but at a lower incidence than in the teratology study. There was no evidence of significant effects on the physical development, survival, behavior and reproductive performance of the F₁ generation or on the development and survival of the F₂ generation pups resulting from treatment of the F₀ females with celecoxib.

3.2.3 Mutagenicity

Celecoxib produced no evidence of mutagenicity in vitro in bacteria (Ames assay) or mammalian cells. Both assays evaluated concentrations of celecoxib that were delimited by cytotoxicity or signs that the solubility limits of the compound had been exceeded. No evidence of mutagenic potential, clastogenicity, or potential for disruption of the mitotic apparatus was detected in vivo; and no direct signs of clastogenicity were observed in vitro. The positive and negative controls for all assays yielded the expected results, thus validating the integrity of the test systems and establishing that celecoxib is not genotoxic. This conclusion is consistent with the absence of carcinogenicity in the cancer bioassays.

3.3 Nonclinical Pharmacokinetics

Nonclinical assessment of the PK of celecoxib was conducted in five species. Celecoxib is well absorbed following oral administration to animals with an absolute bioavailability of 60-90%. The apparent volume of distribution of celecoxib was approximately 2 to 3 L/kg and was consistent across the species examined. This volume is greater than total water volume and suggests the drug is readily available to tissues. Celecoxib was eliminated rapidly from the plasma of guinea pig, cynomolgus monkey and rhesus monkey with half-lives of 1-2 hours. Celecoxib crosses the placenta and is available to the fetus. Celecoxib is excreted in rat milk at concentrations similar to those in serum.

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4.0 HUMAN PHARMACOKINETICS

Pharmacokinetic data were obtained from over 1500 subjects/patients who received single or multiple oral doses of celecoxib in 32 clinical studies (Table 1).

Table 1. Summary of Celecoxib Pharmacokinetic Studies

Type of Data	Study	Basic PK Profile	No. of Subjects
Basic PK Profile	001	Single-dose Safety/Tol/PK	52
	400	Single-dose Safety/Tol/PK (Japan)	30
	003	Multiple-dose Safety/Tol/PK	24
	004	Multiple-dose Safety/Tol/PK	24
	401	Multiple-dose Safety/Tol/PK (Japan)	6
	006	[¹⁴ C]-Celecoxib ADME	8
	019	Food and Antacid Effects	24
	026	Platelet Effect/PK 400 mg BID	6
	032	Total vs. Unbound Conc.	8
	037	Capsule vs. Suspension Bioavail.	36
	043	BID vs. QD Dosing	24
	065	Platelet Function/PK 600 mg BID	12
	069	AM vs. PM QD Dosing	24
	088	Fed/Fasting 50 mg vs. Fed/Fasting 100 mg	24
Special Populations	010	PK/Renal Effect in Elderly	24
	015	Elderly vs. Young PK	48
	016	PK in Hepatic Impairment	46
	036	PK in Chronic Renal Failure	22
	012	PK in RA	181
	013	PK in OA	170
	824	Population PK Phase III (studies 020 and 023)	110
	826	Dental Pain PK/PD (studies 005, 025, 027, 070)	427
Drug-Drug Interactions	017	Methotrexate Interaction	14
	038	Lithium Interaction	24
	072	Fluconazole/Ketoconazole Interaction	35
	040	Warfarin Interaction	12
	050	Phenytoin Interaction	16
	051	Tolbutamide Interaction	16
	039	Glyburide Interaction	24
Bioequivalency of Clinical Trial and Commercial Formulations	018	Phase II vs. Phase III 200 mg	24
	044	Phase III vs. Commercial 200 mg	24
	084	2*100 mg Phase III vs. 2*100 mg Commercial vs. 1*200 mg Commercial	47

4.1 Pharmacokinetic Profile

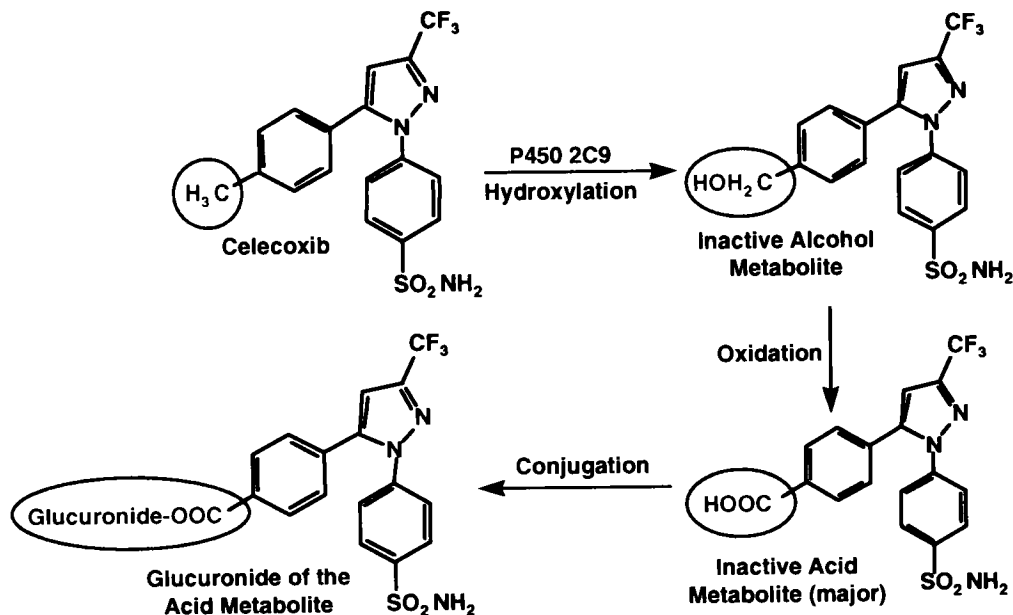
Celecoxib has an apparent plasma clearance of ~500 ml/min (30 L/hr) adjusted for 70 kg body weight in young healthy adults following single dose administration. It has a protein binding in vivo of about 97% and this binding remains constant within the wide therapeutic concentration range of the total drug. It is equally distributed between plasma and erythrocytes. The apparent volume of distribution of celecoxib was ~500 L/70 kg after a single 200 mg dose in young healthy adults, suggesting extensive tissue uptake. The plasma elimination half life of celecoxib is ~10-12 hr. The absorption of celecoxib is slightly increased when taken with food and slightly decreased in the presence of antacids. These effects, however, are not considered clinically important and do not require dose adjustment. There is also circadian variation in the absorption of celecoxib resulting in slower absorption of the drug after evening dosing compared to morning dosing. Time of once-daily celecoxib administration (morning vs. evening) did not affect total drug exposure over 24 hours. However, once-daily dosing in the evening resulted in a slower rate of absorption and would be expected to provide higher drug concentrations in the morning.

4.2 Metabolism

Celecoxib is extensively metabolized in man and none of the metabolites is pharmacologically active (Figure 3). The percentage of dose excreted in feces as unchanged drug is only 2.6% and no unchanged drug was detected in urine.

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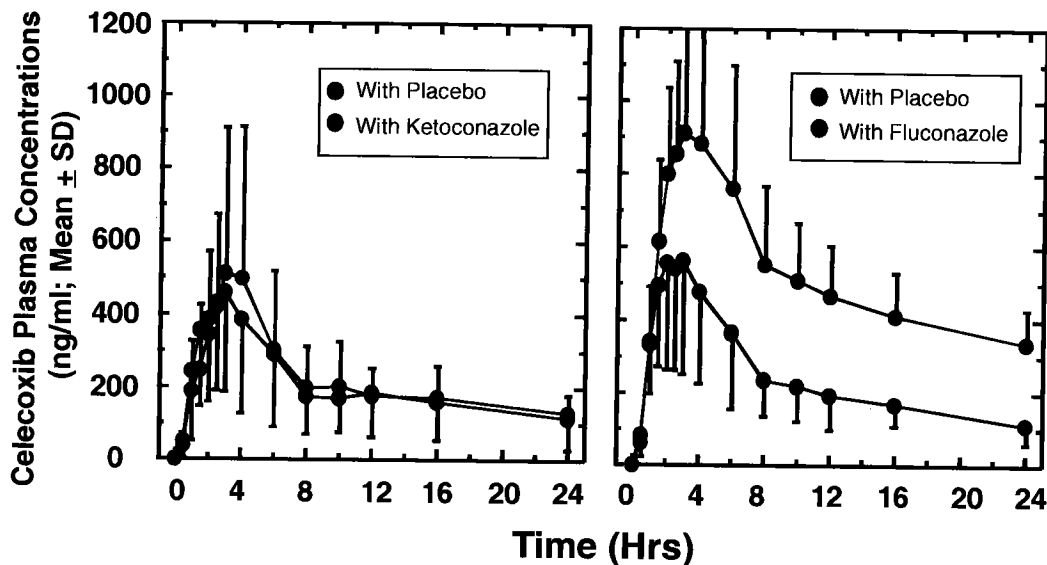
Figure 3. Metabolic Profile of Celecoxib



The major excreted material is the inactive acid metabolite which constitutes ~19% of the dose in the urine and ~54% in the feces. This acid metabolite is formed from the initial and the rate determining hydroxylated metabolite. Both in vitro and in vivo studies indicate that this hydroxylation pathway is mediated predominantly via cytochrome P450 2C9. This was demonstrated clinically by assessing the metabolism of celecoxib in the presence of the cytochrome P450 3A4 inhibitor ketoconazole (200 mg QD for seven days) or the cytochrome P450 2C9 inhibitor fluconazole (200 mg QD for seven days) (Figure 4). Ketoconazole treatment did not markedly increase plasma concentrations of celecoxib whereas fluconazole produced nearly a two-fold increase in the area under the curve of celecoxib.

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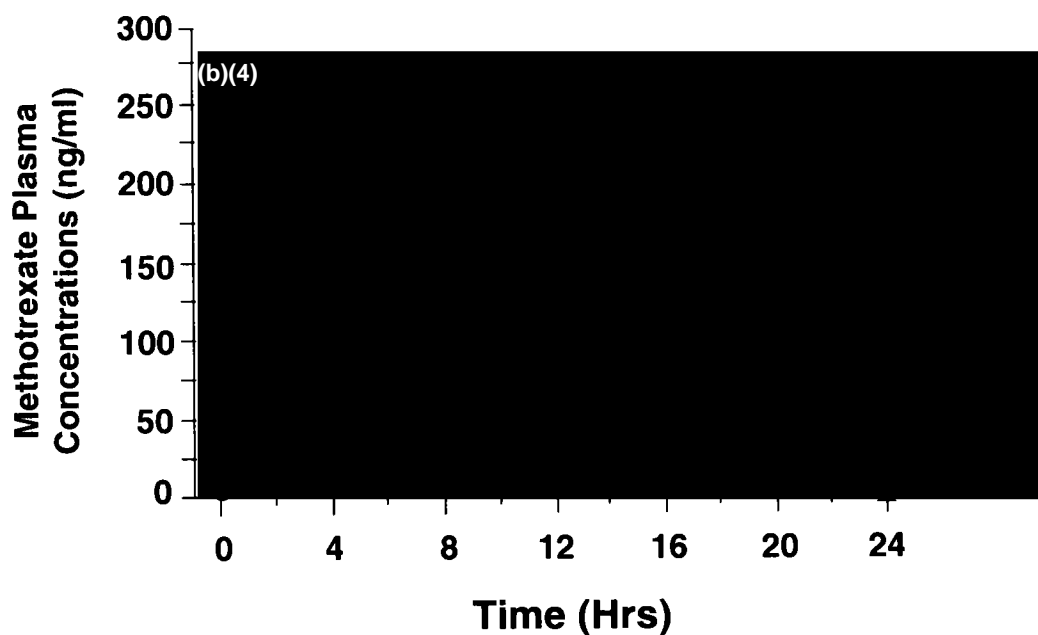
Figure 4. Effects of Multiple Oral Doses of Ketoconazole and Fluconazole on the Single-Dose PK of Celecoxib: Study 072



4.3 Drug-Drug Interactions

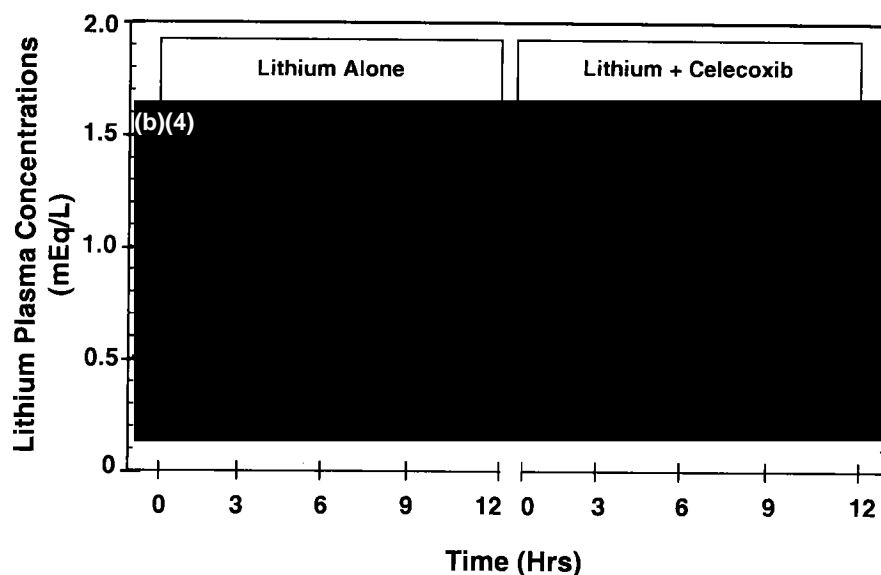
Drug-drug interaction studies were done to examine the effects of multiple doses of celecoxib on the PK of other known substrates of cytochrome P450 2C9 with narrow therapeutic windows. The cytochrome P450 2C9 substrates chosen were tolbutamide, phenytoin, glyburide and warfarin. It is noteworthy that all of these drugs have been reported to interact with some of the presently available NSAIDs. Because of their COX-1 mediated effect on the kidney, some of the NSAIDs have also been reported to decrease the renal clearance of those drugs that are predominantly eliminated via the kidney. (4) Effects of celecoxib on the renal clearance of methotrexate and lithium were therefore also examined. Celecoxib administered as 200 mg twice a day (BID) for seven days did not significantly affect the kinetics of methotrexate (Figure 5).

Figure 5. Effect of Multiple Oral Doses of Celecoxib on Methotrexate PK in Rheumatoid Arthritis Patients Receiving Weekly Oral Doses of Methotrexate: Study 017



Serum concentrations of lithium increased slightly (17%) when coadministered with celecoxib (200 mg BID for seven days) but this increase was not considered clinically important (Figure 6). In all subjects who received lithium and celecoxib, lithium plasma concentrations did not exceed the upper range of therapeutic lithium concentration (1.5 mEq/L).

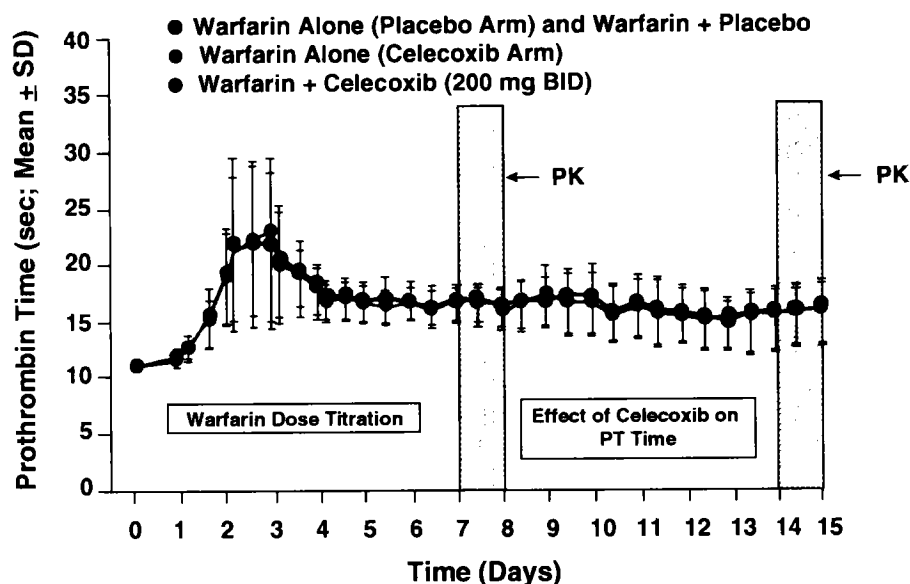
Figure 6. Effect of Multiple Oral Doses of Celecoxib on the Steady State PK of Lithium: Study 038



Ranges for normal limits are shown by dotted lines

Multiple doses of celecoxib also showed no clinically important interactions with other substrates of cytochrome P450 2C9, namely phenytoin, glyburide, tolbutamide and S-warfarin. Figure 7 shows no change in prothrombin time following multiple doses of warfarin administered with placebo compared to warfarin administered with celecoxib 200 mg BID for seven days.

Figure 7. Prothrombin Time vs. Time Relationship Following Administration of Racemic Warfarin During Dose Titration Phase and During Placebo or Celecoxib Coadministration: Study 040



4.4 Pharmacokinetics in Special Populations

The clearance of celecoxib is lower (higher drug exposure [area under the plasma concentration-time curve]) in elderly women and in patients with moderate hepatic impairment (Figures 8 and 9). The reduction in clearance seen in elderly females (>65 years) in the PK studies can be partly attributed to age and partly to their lower body weight. However, the decrease in clearance in healthy elderly Caucasians is <40% compared to healthy Caucasians <50 years. Population PK analysis of patients included in the pivotal arthritis efficacy trials indicated that body weight and race had important influences on the clearance in OA and RA patients. Celecoxib clearance is not markedly reduced in patients with stable chronic renal dysfunction (glomerular filtration rate [GFR] >34 ml/min/1.73 m²) and in patients with Type II non-insulin dependent diabetes mellitus (NIDDM).

Figure 8. Steady State Plasma Concentrations in Patients with Mild and Moderate Hepatic Impairment and Their Matching Controls: Study 016

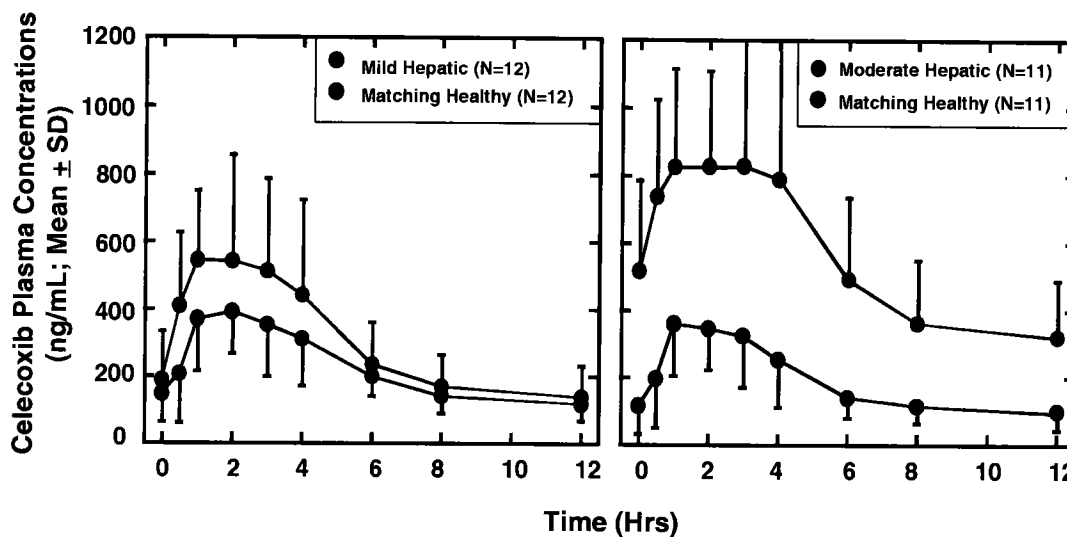
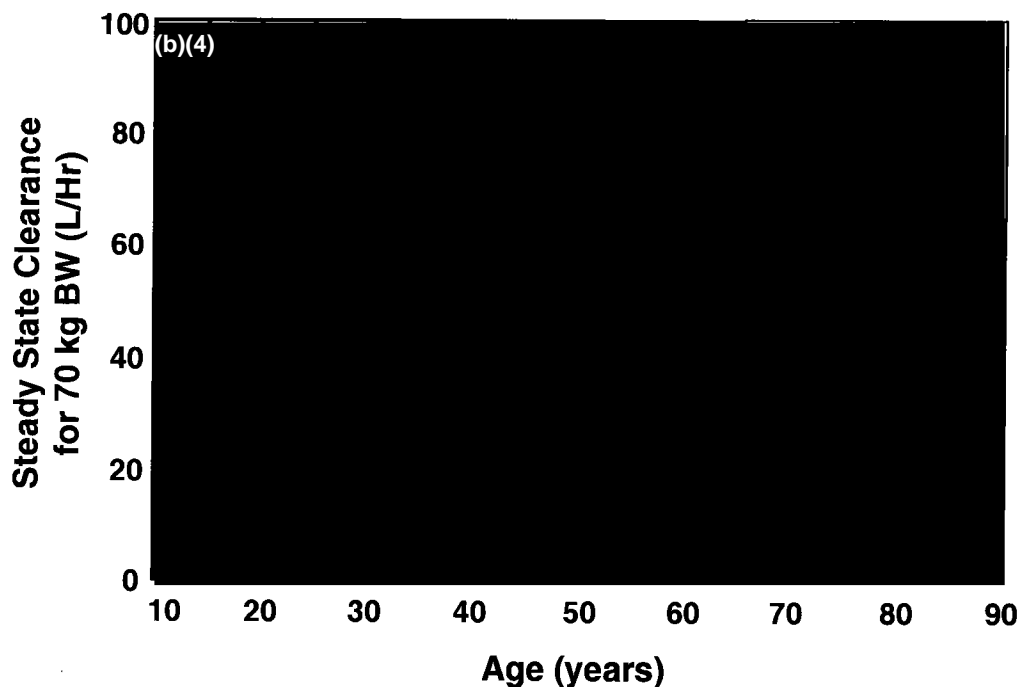


Figure 9. Relationship Between Age and 70 kg Body Weight Adjusted Steady State Clearance Following 200 mg BID Administration of Celecoxib Given with Food: Studies 010, 015, 017, and 043



5.0 CLINICAL EFFICACY

5.1 Efficacy in Osteoarthritis

Eleven studies, five pivotal, five supportive, and one open-label, long-term safety study were conducted in patients with OA to provide evidence of the efficacy of celecoxib for the treatment of the signs and symptoms of OA (Table 2). The data presented in this section are primarily from the pivotal OA efficacy trials (Studies 020, 021, 054, 060, and 087), which were all double-blind, placebo-controlled trials of 6 or 12 weeks duration, and enrolled 200 or more patients per treatment. The five supportive controlled trials (Studies 013, 047, 042, 062, and 071) are each summarized briefly.

Table 2. Summary of Celecoxib OA Studies

Study No. - Population	Duration	No. of Patients	Treatments
Pivotal Studies			
020 - Knee OA flare	12 weeks	1093	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
021 - Knee OA flare	12 weeks	1215	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
054 - Hip OA flare	12 weeks	1061	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
060 - Knee OA flare	6 weeks	686	Celecoxib 100 mg BID or 200 mg QD or placebo
087 - Knee OA flare	6 weeks	718	Celecoxib 100 mg BID or 200 mg QD or placebo
Supportive Controlled Studies			
013 - Knee OA flare	2 weeks	293	Celecoxib 40, 100, or 200 mg BID or placebo
047 - Knee OA flare	4 weeks	402	Celecoxib 25, 100, or 400 mg BID or placebo
042 - Hip or knee OA	6 weeks	688	Celecoxib 100 mg BID or diclofenac 50 mg BID
062 - OA or RA	12 weeks	537 (389 OA)	Celecoxib 200 mg BID or naproxen 500 mg BID
071 - OA or RA	12 weeks	1099 (812 OA)	Celecoxib 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID
Open-Label Study			
024 - OA or RA	1-2 years	4499 (2554 OA)	Celecoxib 100-200 mg BID for OA

5.1.1 Pivotal OA Efficacy Studies: Studies 020, 021, 054, 060 and 087

5.1.1.1 Population and Design

Each of the three 12-week pivotal studies (Studies 020, 021, and 054) was a randomized, multicenter, double-blind, active- and placebo-controlled comparison study of the efficacy and safety of celecoxib 50 mg BID, 100 mg BID, and 200 mg BID and naproxen 500 mg BID in patients with OA of the knee (Studies 020 and 021) or hip (Study 054).

The two 6-week pivotal studies (Studies 060 and 087) were conducted to assess whether a once-a-day dose regimen was appropriate and both were randomized, parallel group, multicenter, double-blind, placebo-controlled studies comparing the efficacy of celecoxib 200 mg QD to celecoxib 100 mg BID in patients with OA of the knee.

In all pivotal studies, patients were to be in an OA flare at the Baseline Visit. The criteria for demonstrating OA flare depended on whether the patient was in Category 1 (i.e., currently receiving NSAID or analgesic therapy for his/her OA) or Category 2 (i.e., not receiving NSAID or analgesic therapy and had uncontrolled OA).

For patients in Category 1, an OA flare was demonstrated if both the Baseline Patient's and the Physician's Global Assessment of Arthritic Condition were rated as "fair," "poor" or "very poor" and the Baseline arthritis assessments met at least three of the following four criteria:

1. Patient's Assessment of Arthritis Pain (Visual Analog Scale [VAS]) measurement of at least 40 mm (on a 100 mm scale);
2. An increase from the screening assessment of two or more points in the OA Severity Index (on a 24 point scale);
3. An increase from the screening visit of one or more grades in the Patient's Global Assessment of Arthritic Condition (on a 5 point scale);
4. An increase from the screening visit of one or more grades in the Physician's Global Assessment of Arthritic Condition (on a 5 point scale).

For patients in Category 2, an OA flare was demonstrated if they met at least three of the following four criteria during the Baseline arthritis assessments:

1. Patient's Assessment of Arthritis Pain (VAS) measurement of at least 40 mm;
2. The OA Severity Index was ≥ 7 ;
3. The Patient's Global Assessment of Arthritic Condition was "poor" or "very poor";
4. The Physician's Global Assessment of Arthritic Condition was "poor" or "very poor."

5.1.1.2 Scales Used for Measurement of OA Efficacy

The analysis of celecoxib's efficacy in the treatment of the signs and symptoms of OA incorporated data from a large number of primary and secondary endpoints.

The primary OA efficacy endpoints included the following:

- Patient's Assessment of Arthritis Pain - VAS (15)
- Patient's Global Assessment of Arthritic Condition (16)
- Physician's Global Assessment of Arthritic Condition (16)
- WOMAC (Western Ontario and McMaster Universities) OA Index (Composite score and subscores for pain, joint stiffness, and physical function) (17)

The final list of secondary OA efficacy endpoints included the following:

- Functional Capacity Classification (18)
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- OA Severity Index (OASI) (19)
- APS (American Pain Society) Pain Measure (in 12-week pivotal OA studies only) (20)
- Patient Assessment of Function

In addition, the SF-36 Health Survey was used to obtain quality-of-life information. (21)

Primary efficacy evaluations were measured at Baseline, Weeks 2, 6, and 12 (or Early Termination) in each of the 12-week pivotal studies and at Baseline and Weeks 2 and 6 (or Early Termination) in each of the 6-week pivotal studies. The WOMAC OA Index was measured at Baseline, and Weeks 2 and 12 in each of the 12-Week pivotal studies and Baseline and Week 6 in each of the 6-week pivotal studies.

The primary population for analysis was the Intent-to-Treat (ITT) cohort which was defined as all randomized patients who took at least one dose of the study drug. The last observation carried forward (LOCF) method was used for imputing missing values.

The Patient's and Physician's Global Assessments of Arthritic Condition were made independently and were graded on a 5 point scale (5-very poor, 4-poor, 3-fair, 2-good, or

1-very good). The Patient's Assessment of Arthritis Pain - VAS was assessed for patient-identified "Index Joint" (i.e., the hip or knee with the most symptoms of OA). Patients assessed the amount of arthritis pain in the "Index Joint" on a 100 mm line VAS with the 0 mm point indicating no pain and 100 mm point indicating the most severe pain. The WOMAC OA Index is a tri-dimensional, self-administered questionnaire. The patient responded to 24 component items: 5 regarding pain, 2 regarding stiffness, and 17 regarding physical function.

Mean change from baseline analyses using analysis of covariance models were performed for Patient's Assessment of Arthritis Pain and the WOMAC OA Index. For Patient's and Physician's Global Assessments, patients were classified into 'Improved,' 'No Change', and 'Worsened' categories based on a two grade change criterion. Improvement was defined as reduction of at least two grades from Baseline for grades 3-5 or a change in grade from 2 to 1. A categorical analysis based on the Cochran-Mantel-Haenszel test was performed for treatment comparisons.

5.1.1.3 Patient Disposition

A total of 3255 patients with OA of either the hip or knee were entered into one of the three 12-week pivotal studies (020, 021, and 054), were randomized to receive one of five treatments: celecoxib 50 mg BID, celecoxib 100 mg BID, celecoxib 200 mg BID, naproxen 500 mg BID, or placebo, and were included in the ITT cohort. Table 3 presents a summary of all patients, by treatment group, who completed one of the three 12-week pivotal studies. The reasons for study termination are also summarized in this table.

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Table 3. Reasons for Study Termination: 12-Week Pivotal OA Studies 020, 021, and 054

Study	Number of OA Patients by Treatment Group				
	Placebo	Celecoxib			Naproxen
		50 mg BID	100 mg BID	200 mg BID	500 mg BID
Study 020 (a)	(N=204)(b)	(N=203)	(N=197)	(N=202)	(N=198)
Total Completed	91 (45%)	118 (58%)	116 (59%)	129 (64%)	116 (59%)
Total Withdrawn	113 (55%)	85 (42%)	81 (41%)	73 (36%)	82 (41%)
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)
Adverse Event	16 (8%)	18 (9%)	31 (16%)	21 (10%)	18 (9%)
Other	18 (9%)	6 (3%)	10 (5%)	3 (1%)	12 (6%)
Study 021 (a)	(N=242)	(N=252)	(N=240)(b)	(N=233)	(N=226)
Total Completed	119 (49%)	168 (67%)	165 (69%)	154 (66%)	147 (65%)
Total Withdrawn	123 (51%)	84 (33%)	75 (31%)	79 (34%)	79 (35%)
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)
Adverse Event	14 (6%)	16 (6%)	16 (7%)	23 (10%)	30 (13%)
Other	20 (8%)	12 (5%)	8 (4%)	7 (3%)	9 (4%)
Study 054	(N=218)(b)	(N=216)	(N=207)	(N=213)	(N=207)
Total Completed	79 (36%)	111 (51%)	111 (54%)	119 (56%)	118 (57%)
Total Withdrawn	139 (64%)	105 (49%)	96 (46%)	94 (44%)	89 (43%)
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)
Adverse Event	16 (7%)	7 (8%)	27 (13%)	25 (12%)	29 (14%)
Other	10 (5%)	12 (6%)	8 (4%)	14 (7%)	9 (4.3%)

a) Includes only patients with OA of the knee. Eighty-nine patients with OA of the hip were enrolled in Study 020; 22 patients with OA of the hip were enrolled in Study 021.

b) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]), who were randomized into a study but did not receive study medication and are not included in the ITT cohort.

A total of 1399 patients with OA of the knee were entered into one of the two 6-week pivotal studies, were randomized to receive one of three treatments (celecoxib 100 mg BID, celecoxib 200 mg QD, or placebo), and were included in the ITT cohort. Table 4 presents a summary of all patients, by treatment group, who completed one of the 6-week pivotal studies. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.

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Table 4. Reasons for Study Termination : 6-Week Pivotal OA Studies 060 and 087

Study	Number of OA Patients by Treatment Group		
	Placebo	Celecoxib	
		100 mg BID	200 mg QD
Study 060	(N=232)(a)	(N=231)	(N=223)(a)
Total Completed	146 (63%)	194 (84%)	182 (82%)
Total Withdrawn	86 (37%)	37 (16%)	41 (18%)
Treatment Failure	56 (24%)	18 (8%)	21 (9%)
Adverse Event	20 (9%)	11 (5%)	9 (4%)
Other	10 (4%)	8 (3%)	11 (5%)
Study 087	(N=244)(b)	(N=243)^b	(N=231)
Total Completed	164 (67%)	194 (80%)	191 (83%)
Total Withdrawn	80 (33%)	49 (20%)	40 (17%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 (5%)	9 (4%)	6 (3%)
Other	13 (5%)	13 (5%)	10 (4%)

a) One placebo patient and one celecoxib 200 mg QD patient were randomized but did not receive study medication.

b) One placebo patient and two celecoxib 100 mg BID patients were randomized but did not receive study medication.

5.1.1.4 Patient Characteristics

Tables 5 and 6 show descriptive summaries of the pooled Baseline demographic characteristics and arthritis history for all patients enrolled in the 12- and 6-week pivotal OA trials, respectively. In these studies, age, race, gender, and arthritis history were similar across treatment groups. The demographic characteristics and arthritis history for each individual study were also consistent with the pooled summaries with no differences across treatment groups.

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Table 5. Baseline Demographic Characteristics and Disease Status: Pooled 12-Week Pivotal OA Studies 020, 021, and 054

Baseline Demographic Characteristic	Placebo (N=664)(a)	Celecoxib			Naproxen 500 mg BID (N=631)
		50 mg BID (N=671)	100 mg BID (N=644)(a)	200 mg BID (N=648)	
Age (years)					
Mean (Std. Dev.)	62.3 (10.22)	61.6 (11.09)	61.9 (11.31)	61.9 (11.43)	62.7 (11.09)
Range	(b)(4)				
≥65 years - N (%)	303 (46%)	293 (44%)	286 (44%)	295 (46%)	297 (47%)
Race/Ethnic Origin					
Caucasian/ Hispanic - N (%)	599 (90%)	587 (87%)	576 (89%)	573 (88%)	564 (89%)
Black - N (%)	59 (9%)	80 (12%)	63 (10%)	71 (11%)	65 (10%)
Other - N (%)	6 (1%)	4 (1%)	5 (1%)	4 (1%)	2 (<1%)
Gender					
Female - N (%)	466 (70%)	444 (66%)	441 (68%)	451 (70%)	430 (68%)
Disease Duration - Years					
Mean (Std. Dev.)	9.0 (8.93)	8.4 (8.18)	8.6 (8.00)	8.5 (8.44)	8.8 (8.84)
Range	(b)(4)				
≥5 years - N (%)	407 (61%)	390 (58%)	389 (60%)	375 (58%)	367 (58%)

a) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]) who were randomized into a study but did not receive study medication and are not included in the ITT cohort.

Table 6. Baseline Demographic Characteristics and Disease Status: Pooled 6-Week Pivotal OA Studies 060 and 087

Baseline Demographic Characteristic	Placebo (N=476) (a)	Celecoxib	
		100 mg BID (N=474)	200 mg QD (N=454)
Age (years)(b)			
Mean (Std. Dev.)	61.9 (11.49)	62.5 (11.16)	62.0 (11.59)
Range	(b)(4)		
≥65 years - N (%)	215 (45%)	220 (46%)	197 (43%)
Race/Ethnic Origin			
Caucasian/Hispanic - N (%)	425 (89%)	417 (88%)	398 (88%)
Black - N (%)	42 (9%)	50 (11%)	41 (9%)
Other - N (%)	8 (2%)	6 (1%)	15 (3%)
Gender			
Female - N (%)	333 (70%)	321 (68%)	306 (67%)
Disease Duration - Years			
Mean (Std. Dev.)	9.1 (8.47)	9.4 (8.79)	9.1 (7.92)
Range	(b)(4)		
≥5 years - N (%)	304 (64%)	316 (67%)	305 (67%)

a) Total number of patients includes five patients (one in the placebo group [Study 060], one in the placebo group [Study 087], one in the celecoxib 200 mg QD group [Study 060] and two in the celecoxib 100 mg BID group [Study 087]) who were randomized into a study but did not receive study medication and are not included in the ITT cohort.

b) n=475 for age.

5.1.1.5 Efficacy and Dose Response

5.1.1.5.1 Twelve-Week Pivotal Trials: Studies 020, 021 and 054

As shown by the Patient's Assessment of Arthritis Pain (VAS), Celecoxib 100 mg BID and 200 mg BID produced statistically significantly greater improvement compared to placebo by Week 2 and continuing through Week 12 in each of the 12-week pivotal OA

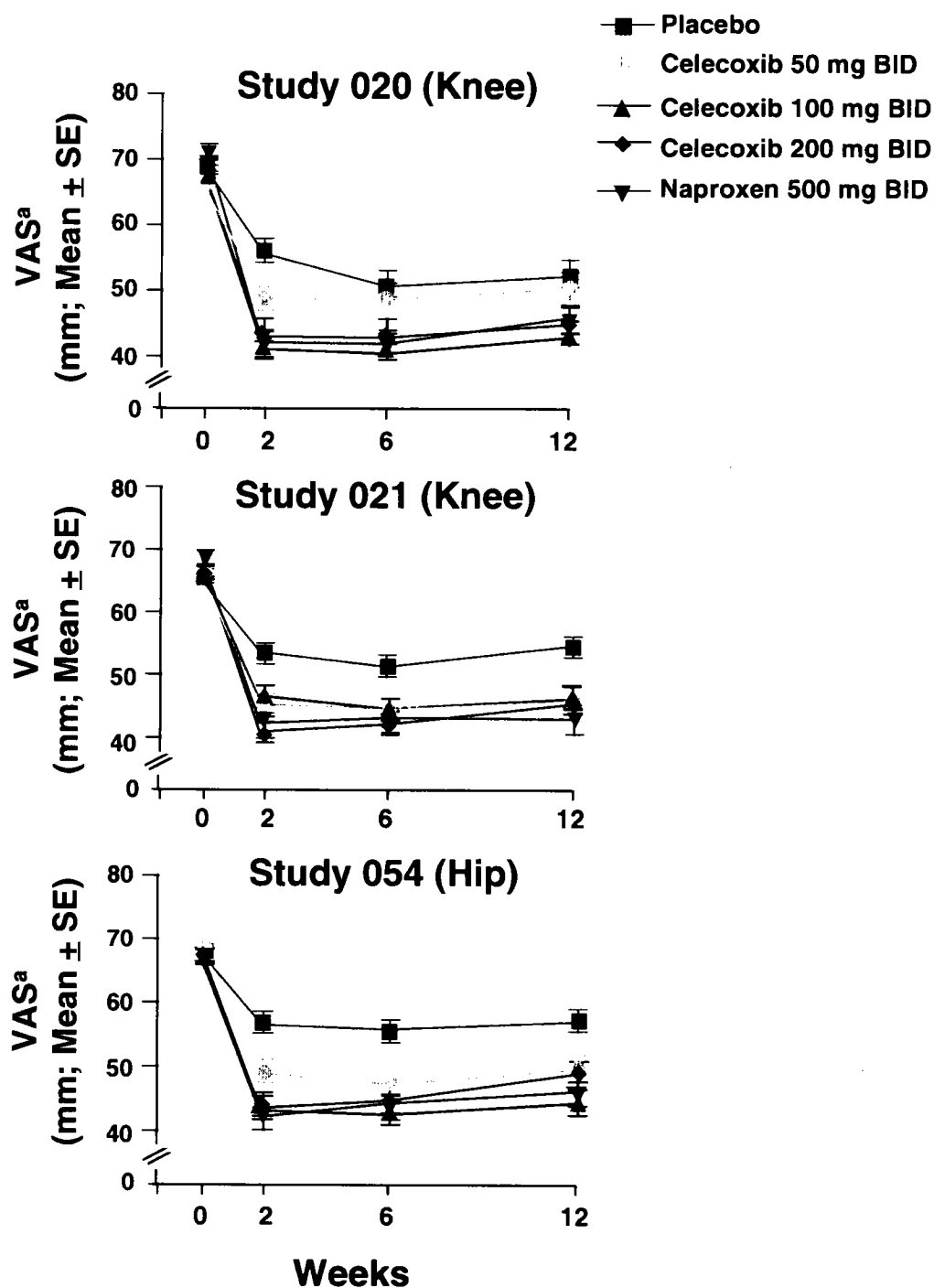
studies (Figure 10 and Table 7). Celecoxib 50 mg BID was also efficacious in two of these studies (Studies 021 and 054). In the other primary measures of efficacy, all doses of celecoxib were efficacious in each of the three pivotal 12-week studies (Figure 11 and Tables 8 and 9). Significant improvement was observed at Week 12 as well as earlier assessments with the exception of the Physician's Global Assessment for celecoxib 50 mg BID at Week 2 in Study 021.

For all primary measures of efficacy across the three pivotal 12 week studies, celecoxib doses of 100 and 200 mg BID produced a similar degree of improvement in OA patients (Tables 7, 8, and 9). No statistically significant differences between these doses were present at any assessment time for any measure of efficacy with one exception. A statistically significant difference occurred in Study 021 for the Patient's Assessment of Arthritis Pain (VAS) at Week 2 where the response was greater with celecoxib 200 mg BID compared to celecoxib 100 mg BID. The results indicate that celecoxib 100 mg BID is the full therapeutic dose for treating the signs and symptoms of OA and that increasing the dose to 200 mg BID provides no further benefit of improved efficacy.

The responses to celecoxib 100 mg BID and 200 mg BID were comparable to naproxen 500 mg BID for all primary measures of efficacy at all assessment times in all three 12-week pivotal studies with few exceptions (Tables 7, 8, and 9). In Study 020, the response to celecoxib 100 mg BID as determined by the WOMAC OA Index - Pain subscale was significantly greater than naproxen at Week 12 (Table 9). In Study 021, the response to naproxen was significantly greater than celecoxib 100 mg BID at Weeks 2 and 12 for Patient's Assessment of Arthritis Pain (VAS) (Table 7).

Although 50 mg BID provides efficacy in OA when compared to placebo, a consistent pattern emerges indicating that this dose is submaximally efficacious. The responses to celecoxib 50 mg BID were statistically significantly lower when compared to celecoxib doses of either 100 mg BID or 200 mg BID or naproxen 500 mg BID in Studies 020, 021, and 054 for many of the primary efficacy measures at one or more assessment times.

Figure 10. Patient's Assessment of Arthritis Pain: 12-Week Pivotal OA Studies 020, 021 and 054



a) Visual analog scale ranges from 0 (no pain) to 100 mm (most severe pain).

Table 7. Patient's Assessment of Arthritis Pain - VAS (Change in Least Square (LS) Mean Score from Baseline): 12-Week Pivotal OA Studies 020, 021 and 054

Studies 020, 021 and 054

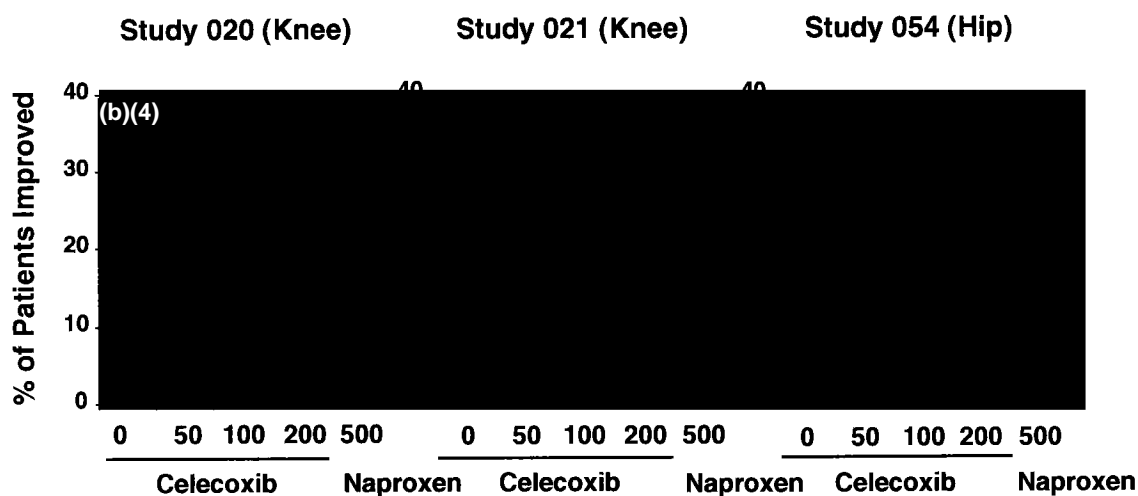
Treatment Group	N	Baseline LS Mean	LS Mean Change		
			Week 2	Week 6	Week 12
Study 020					
Placebo	201	69.5	-12.1	-16.6	-15.1
Celecoxib 50 mg BID	203	67.0	-18.4*	-17.9	-16.0
Celecoxib 100 mg BID	196	68.4	-26.1*‡	-25.9*‡	-23.1*‡
Celecoxib 200 mg BID	201	69.1	-24.6*‡	-24.5*‡	-22.1*‡
Naproxen 500 mg BID	197	71.6	-27.3*‡	-27.0*‡	-22.7*‡
Study 021					
Placebo	242	65.9	-12.9	-14.6	-12.0
Celecoxib 50 mg BID	252	66.6	-21.5*	-21.7*	-20.3*
Celecoxib 100 mg BID	238	66.3	-20.3*†	-21.7*	-19.6*†
Celecoxib 200 mg BID	233	66.4	-26.4*‡	-24.1*	-21.0*
Naproxen 500 mg BID	226	68.5	-26.6*‡	-25.0*	-25.3*‡
Study 054					
Placebo	217	68.2	-11.8	-13.2	-11.1
Celecoxib 50 mg BID	216	68.4	19.7*	-21.5*	-19.0*
Celecoxib 100 mg BID	207	67.1	-24.4*‡	-25.1*	-23.3*
Celecoxib 200 mg BID	212	67.3	-24.4*‡	-23.9*	-19.3*
Naproxen 500 mg BID	207	67.3	-26.5*‡	-24.8*	-22.3*

* Significantly different from placebo; p<0.05.

† Significantly different from naproxen; p<0.05.

‡ Significantly different from celecoxib 50 mg BID; p<0.05.

Figure 11. Patient's Global Assessment at Week 12: 12-Week Pivotal OA Studies 020, 021 and 054



* Significantly different from placebo; p<0.05.

Doses are mg BID

Table 8. Percent of Patients Improved from Baseline for Primary (Categorical) OA Efficacy Variables: 12-Week Pivotal OA Studies 020, 021 and 054

Treatment Group	Study 020		Study 021		Study 054	
	N	% Improved(a) at Week 12	N	% Improved(a) at Week 12	N	% Improved(a) at Week 12
Patient's Global Assessment of Arthritic Condition (Categorical Change)						
Placebo	203	24	242	22	217	17
Celecoxib 50 mg BID	203	27*	252	34*	216	26*
Celecoxib 100 mg BID	197	35*	239	31*	207	31*
Celecoxib 200 mg BID	202	36*	233	36*	213	29*
Naproxen 500 mg BID	198	29*	226	37*	207	34*
Physician's Global Assessment of Arthritic Condition (Categorical Change)						
Placebo	203	21	242	21	217	18
Celecoxib 50 mg BID	203	30*	252	32*	216	27*
Celecoxib 100 mg BID	197	36*	239	31*	207	32*
Celecoxib 200 mg BID	202	32*	232	31*	213	30*
Naproxen 500 mg BID	198	33*	226	34*	207	32*

* Significantly different from placebo; p<0.05.

a) Improvement is defined as reduction of at least 2 grades from Baseline for grades 3-5 or a change in grade from 2 to 1.

Table 9. WOMAC Composite Score and Subscales: 12-Week Pivotal OA Studies 020, 021 and 054

Treatment (mg BID dose)	Study 020			Study 021			Study 054		
	N	Baseline	Change at Week 12	N	Baseline	Change at Week 12	N	Baseline	Change at Week 12
WOMAC OA Index: Composite Score (Change in LS Mean Score from Baseline)									
Placebo	182	51.6	-5.6	240	50.6	-5.4	217	51.2	-4.6
Celecoxib 50 mg	174	51.6	-9.6*	247	51.9	-12.9*	214	49.4	-8.0*
Celecoxib 100 mg	175	50.4	-13.6*†	237	52.1	-12.0*	207	50.6	-10.3*
Celecoxib 200 mg	181	50.9	-12.1*	230	50.1	-11.5*	211	51.2	-11.0*†
Naproxen 500 mg	177	52.6	-11.3*	225	52.6	-13.9*	205	50.4	-12.4*†
WOMAC OA Index: Pain Subscale (Change in LS Mean Score from Baseline)									
Placebo	201	10.9	-1.2	242	10.6	-1.4	217	10.7	-1.0
Celecoxib 50 mg	197	10.7	-2.0*	248	10.8	-2.8*	215	10.5	-1.7*
Celecoxib 100 mg	196	10.5	-3.1*†	237	10.8	-2.6*	207	10.7	-2.2*
Celecoxib 200 mg	201	10.7	-2.7*†	232	10.4	-2.5*	211	10.9	-2.4*†
Naproxen 500 mg	198	11.0	-2.4*	226	11.1	-3.0*	207	10.6	-2.7*†
WOMAC OA Index: Joint Stiffness Subscale (Change in LS Mean Score from Baseline)									
Placebo	202	4.8	-0.5	242	4.8	-0.5	217	4.7	-0.4
Celecoxib 50 mg	197	4.8	-0.9*	248	4.8	-1.2*	216	4.7	-0.8*
Celecoxib 100 mg	196	4.6	-1.2*†	237	4.8	-1.1*	207	4.7	-1.0*
Celecoxib 200 mg	201	4.9	-1.1*	232	4.8	-1.1*	211	4.7	-1.0*
Naproxen 500 mg	195	5.0	-1.1*	226	4.9	-1.3*	205	4.7	-1.1*†
WOMAC OA Index: Physical Function Subscale (Change in LS Mean Score from Baseline)									
Placebo	184	36.0	-3.9	240	35.2	-3.6	217	35.9	-3.2
Celecoxib 50 mg	174	36.1	-6.8*	250	36.4	-8.9*	215	34.2	-5.5*
Celecoxib 100 mg	176	35.3	-9.5*†	237	36.5	-8.3*	207	35.3	-7.0*
Celecoxib 200 mg	181	35.3	-8.1*	231	35.1	-7.9*	211	35.6	-7.5*†
Naproxen 500 mg	180	36.5	-7.8*	225	36.7	-9.6*	207	35.1	-8.4*†

* Significantly different from placebo; p<0.05.

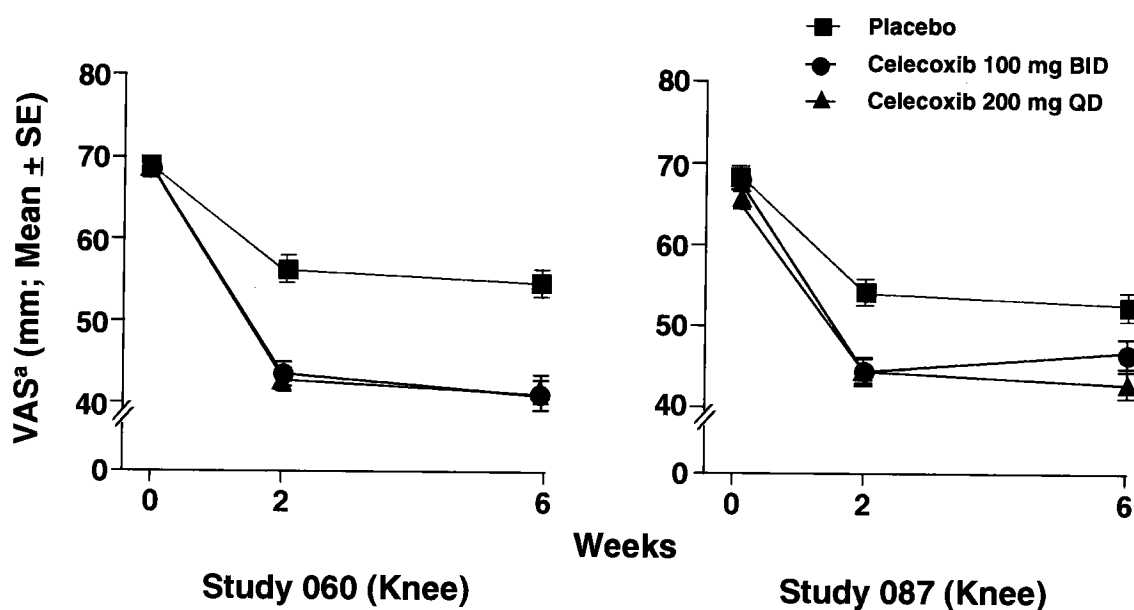
† Significantly different from celecoxib 50 mg BID; p<0.05.

5.1.1.5.2 Six-Week Pivotal Studies: Studies 060 and 087

Celecoxib doses of 100 mg BID and 200 mg QD were statistically significantly superior to placebo in the Patient's Assessment of Arthritis Pain (VAS) at Week 2 and Week 6 in both 6-Week pivotal OA studies (Figure 12 and Table 10). For all other primary measures of efficacy, the responses to celecoxib 100 mg BID and 200 mg QD were also significantly greater than placebo-treated patients at Week 6 (Figure 13, Tables 11 and 12) as well as the Week 2 assessment in both studies. The results obtained with 100 mg BID in Studies 060 and 087 were consistent with those demonstrated in the 12-Week pivotal OA studies (020, 021 and 054) for all primary measures of efficacy.

Celecoxib 100 mg BID and 200 mg QD provided comparable responses as determined by all measures of efficacy in both studies. No statistically significant differences between these two celecoxib dosing regimens were evident with the exception of a statistically significant difference in the Physician's Global Assessment favoring celecoxib 100 mg BID at the Week 2 assessment in Study 087.

Figure 12. Patient's Assessment of Arthritis Pain: 6-Week Pivotal OA Studies 060 and 087



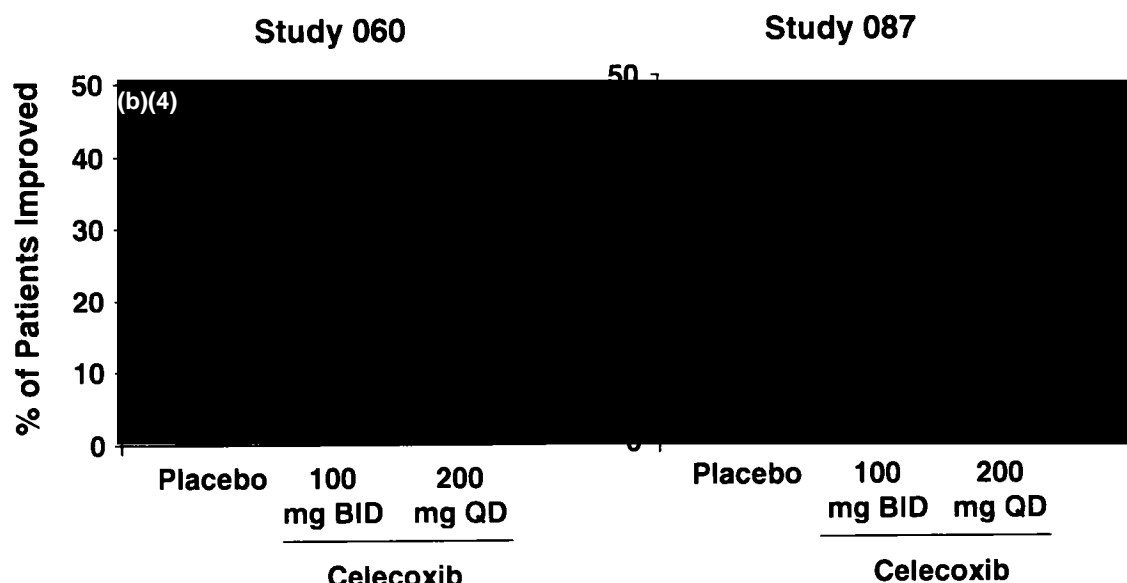
a) Visual analog scale ranges from 0 (no pain) to 100 mm (most severe pain).

Table 10. Patient's Assessment of Arthritis Pain: 6-Week Pivotal OA Studies 060 and 087

Treatment Group	Study 060			Study 087		
	N	Baseline	Change at Week 6	N	Baseline	Change at Week 6
Patient's Assessment of Arthritis Pain: VAS (LS Mean Score)						
Placebo	231	68.6	-14.8	243	68.5	-15.0
Celecoxib 100 mg BID	231	68.1	-28.5*	241	68.0	-21.2*
Celecoxib 200 mg QD	222	68.7	-27.7*	231	65.7	-23.5*

* Significantly different from placebo; p<0.05.

Figure 13. Patient's Global Assessment at Week 6: 6-Week Pivotal OA Studies 060 and 087



* Significantly different from placebo; p < 0.05

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Table 11. Percent of Patients Improved from Baseline – Primary Categorical OA Efficacy Variables: 6-Week Pivotal OA Studies 060 and 087

Treatment Group	Study 060		Study 087	
	N	% Improved(a) at Week 6	N	% Improved(a) at Week 6
Patient's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	26	243	27
Celecoxib 100 mg BID	231	42*	241	37*
Celecoxib 200 mg QD	222	42*	231	38*
Physician's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	25	243	24
Celecoxib 100 mg BID	231	43*	241	35*
Celecoxib 200 mg QD	222	43*	231	35*

* Significantly different from placebo; p<0.05.

a) Improvement is defined as reduction of at least 2 grades from Baseline for grades 3-5 or a change in grade from 2 to 1.

Table 12. WOMAC Composite Score and Subscales: 6-Week Pivotal OA Studies 060 and 087

Treatment Group	Study 060			Study 087		
	N	Baseline	Change at Week 6	N	Baseline	Change at Week 6
WOMAC OA Index: Composite Score (LS Mean Score)						
Placebo	224	50.8	-6.6	243	53.0	-8.1
Celecoxib 100 mg BID	229	50.3	-14.1*	241	51.1	-13.3*
Celecoxib 200 mg QD	219	50.2	-12.8*	231	50.9	-13.9*
WOMAC OA Index: Pain Subscale (LS Mean Score)						
Placebo	231	10.5	-1.5	243	10.7	-1.6
Celecoxib 100 mg BID	230	10.5	-3.1*	241	10.1	-2.6*
Celecoxib 200 mg QD	220	10.5	-2.9*	231	10.2	-3.0*
WOMAC OA Index: Joint Stiffness Subscale (LS Mean Score)						
Placebo	230	4.6	-0.6	243	4.7	-0.8
Celecoxib 100 mg BID	230	4.7	-1.2*	241	4.5	-1.3*
Celecoxib 200 mg QD	220	4.6	-1.2*	231	4.7	-1.2*
WOMAC OA Index: Physical Function Subscale (LS Mean Score)						
Placebo	230	35.7	-4.5	243	37.6	-5.7
Celecoxib 100 mg BID	229	35.1	-9.7*	241	36.4	-9.4*
Celecoxib 200 mg QD	219	35.2	-8.8*	231	36.1	-9.7*

* Significantly different from placebo; p<0.05.

5.1.1.6 Health-related Quality of Life

The SF-36 Health Survey was administered at Baseline and at Weeks 2 and 12 of treatment in the 12-week pivotal OA studies (Studies 020, 021 and 054). The mean scores at Baseline together with mean changes from Baseline to Week 12 for the eight domains of the SF-36 Health Survey for each of these studies are shown in Table 13. Statistically significant improvements in Physical Functioning, Role-Physical, Bodily Pain, Vitality, and Social Functioning were observed with celecoxib 100 mg BID, celecoxib 200 mg BID and naproxen 500 mg BID when compared to placebo across all

three studies. Celecoxib 100 mg and 200 mg BID were also associated with significant improvements in mental health in all studies. A significant treatment effect with naproxen for the mental health domain was observed in two studies. The magnitude of improvement for celecoxib 100 mg BID and celecoxib 200 mg BID was consistent across the studies and similar to naproxen.

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Table 13. Baseline Mean Scores and Mean Changes from Baseline for SF-36 Quality-of-Life Domains: 12-Week Pivotal OA Trials 020, 021 and 054

SF-36 Domain(a) Treatment Group	Study 020		Study 021		Study 054	
	Baseline	Change at Week 12	Baseline	Change at Week 12	Baseline	Change at Week 12
Physical Functioning						
Placebo	34.2	3.9	36.3	3.1	34.4	0.9
Celecoxib 50 mg BID	34.3	6.1	34.9	8.3*	36.5	3.7
Celecoxib 100 mg BID	34.9	10.8*	34.7	6.4	35.7	8.1*
Celecoxib 200 mg BID	34.3	8.7*	36.4	7.7*	32.6	10.0*
Naproxen 500 mg BID	33.2	9.9*	33.0	9.9*	36.1	9.2*
Role Physical						
Placebo	24.5	8.5	24.3	5.6	20.2	4.3
Celecoxib 50 mg BID	27.4	9.5	19.4	21.4*	21.9	8.2
Celecoxib 100 mg BID	26.5	19.1*	24.2	13.7*	22.5	13.1*
Celecoxib 200 mg BID	26.2	17.0*	27.2	15.4*	20.5	14.1*
Naproxen 500 mg BID	25.8	18.6*	21.3	17.2*	25.5	14.3*
Bodily Pain						
Placebo	32.7	5.8	33.9	4.9	31.7	3.2
Celecoxib 50 mg BID	33.8	8.4	32.9	14.7*	33.4	8.0*
Celecoxib 100 mg BID	34.9	14.3*	31.6	13.5*	31.5	11.8*
Celecoxib 200 mg BID	33.4	12.6*	34.5	13.7*	31.7	12.1*
Naproxen 500 mg BID	32.6	14.6*	32.0	15.2*	34.0	12.7*
General Health						
Placebo	60.7	1.6	59.9	0.3	63.0	-1.3
Celecoxib 50 mg BID	61.8	1.4	58.8	3.9*	62.1	1.6*
Celecoxib 100 mg BID	64.3	2.9	59.4	2.7	59.9	1.6
Celecoxib 200 mg BID	60.6	2.6	62.6	1.6	59.7	2.4*
Naproxen 500 mg BID	60.6	4.5*	59.1	3.0	62.7	0.1
Vitality						
Placebo	41.1	1.6	41.8	0.1	39.5	0.2
Celecoxib 50 mg BID	42.9	4.8*	40.2	9.6*	41.6	5.7*
Celecoxib 100 mg BID	43.3	9.4*	40.4	6.7*	39.4	7.2*
Celecoxib 200 mg BID	42.7	5.8*	42.5	7.1*	39.7	4.7*
Naproxen 500 mg BID	40.3	8.0*	37.1	8.4*	41.8	7.2*
Social Functioning						
Placebo	64.4	0.0	64.3	-1.8	61.1	0.0
Celecoxib 50 mg BID	63.3	2.3	61.7	7.7*	63.4	2.6
Celecoxib 100 mg BID	64.4	7.9*	62.0	7.6*	60.4	5.3*
Celecoxib 200 mg BID	68.1	4.2*	64.8	7.2*	61.9	5.9*
Naproxen 500 mg BID	62.9	7.6*	59.8	9.5*	65.5	3.6*
Role Emotional						
Placebo	55.7	1.9	53.9	1.7	51.3	-1.9
Celecoxib 50 mg BID	55.3	3.2	49.7	10.2	50.5	6.4*
Celecoxib 100 mg BID	52.5	13.8*	52.4	9.2	53.2	5.5*
Celecoxib 200 mg BID	58.4	5.8	55.5	8.6*	52.5	4.5
Naproxen 500 mg BID	59.2	5.0	50.8	6.4	55.1	3.6
Mental Health						
Placebo	70.3	-0.6	68.7	0.0	70.9	-1.2
Celecoxib 50 mg BID	71.3	-1.2	69.7	3.6*	70.2	2.7*
Celecoxib 100 mg BID	71.2	3.4*	69.2	3.0*	71.3	2.4*
Celecoxib 200 mg BID	71.3	3.3*	70.6	3.5*	69.4	2.9*
Naproxen 500 mg BID	70.8	2.4*	67.4	3.6*	71.8	0.6

* Significantly different from placebo; $p \leq 0.05$.

a) Scale ranged from 0 to 100 with lower score as worse for all domains.

5.1.2 Supportive OA Efficacy Studies

Data from the pivotal OA efficacy trials were supported by the results of five additional placebo- or active-controlled trials.

5.1.2.1 Placebo-Controlled Studies: Studies 013 and 047

Study 013 was a dose-ranging, randomized, double-blind, placebo-controlled, parallel-group, 2-week study to evaluate the safety and efficacy of celecoxib (40, 100, and 200 mg BID) in treating the signs and symptoms of OA of the knee. Patients were eligible if they had OA of the knee in a flare state, a Functional Capacity Classification of I-III, and had not received any NSAIDs or analgesics in the two days prior to receiving the first dose of study medication. Of the 293 ITT patients, 252 (86.0%) completed all two weeks of the study. For the analyses of primary efficacy endpoints, celecoxib 40 mg BID, 100 mg BID, and 200 mg BID were numerically superior to placebo at most visits and statistically superior at some visits.

Study 047 was a randomized, double-blind, placebo-controlled, parallel group, multicenter, four-week study designed to compare the efficacy of celecoxib 25 mg, 100 mg, and 400 mg BID versus placebo in treating the signs and symptoms of OA of the knee. The study also evaluated the efficacious dose range. Patients with OA of the knee in a flare state and who had not received any NSAIDs and analgesics within 48 hours before the Baseline Arthritis Assessments, were eligible for study participation. Overall, 301 (75.1%) of the 401 ITT patients completed all four weeks of the study. For each primary efficacy endpoint, celecoxib 100 mg BID and 400 mg BID were consistently numerically superior to placebo, and at some timepoints were statistically superior. The efficacy of celecoxib 25 mg BID was not superior to placebo.

5.1.2.2 Active-Controlled Studies: Studies 042, 062 and 071

Study 042 was an international, randomized, double-blind, multicenter, parallel group six-week study designed to evaluate the efficacy and safety of celecoxib 100 mg BID as compared to diclofenac 50 mg BID in treating the signs and symptoms of OA of the hip and/or knee. Patients with OA of the hip and/or knee (as defined by the ACR [American College of Rheumatology] criteria) that had been clinically evident for at least six months, who were anticipated to require continuous treatment with an anti-inflammatory analgesic to control arthritis symptoms for the duration of the study, and were

experiencing symptoms of OA at the time of admission to the study, were eligible for study participation. Overall, 617 (89.8%) of 687 ITT patients completed all six weeks of the study. Analysis of primary efficacy endpoints showed that both celecoxib 100 mg BID and diclofenac 50 mg BID provided clinically significant improvement in the signs and symptoms of OA compared to Baseline values.

Study 062 was a randomized, double-blind, parallel group, multicenter, 12-week study designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID to that of naproxen 500 mg BID in patients with OA or RA. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Among those included in the ITT cohort, 388 were OA patients: 193 celecoxib 200 mg BID patients and 195 naproxen 500 mg BID patients. Overall, 359 (67.0%) of 536 ITT patients completed all 12 weeks of the study. There were no clinically significant differences between the celecoxib 200 mg BID and naproxen 500 mg BID treatment groups in the number of patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, or 12.

Study 071 was a randomized, double-blind, parallel group, multicenter, 12-week study designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Among those included in the ITT cohort, 810 were OA patients: 271 celecoxib 200 mg BID patients, 285 diclofenac 75 mg BID patients, and 254 ibuprofen 800 mg TID patients. There were no clinically significant differences between celecoxib and the other treatment groups for Physician's Global Assessment or Patient's Global Assessment at Weeks 4, 8, or 12.

5.1.3 Conclusions

Based on the results of replicate pivotal trials in OA patients, it is concluded that:

- Celecoxib doses of 100 mg BID, 200 mg QD, and 200 mg BID were efficacious in treating the signs and symptoms of OA.

- Celecoxib doses of 100 mg BID and 200 mg QD demonstrated comparable efficacy.
- There was no therapeutic benefit in increasing the dose above a total daily dose of 200 mg.
- Celecoxib, at efficacious doses, had similar efficacy to full therapeutic doses of NSAIDs.
- Health-related quality of life improvements were observed with full therapeutic doses of celecoxib.

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